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Timing of delivery in women with diabetes in pregnancy

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Abstract

The incidence of both gestational and pre-gestational diabetes is increasing worldwide. The main cause of this increase is likely the concomitant increase in the incidence of global obesity, but in the case of gestational diabetes, changes in the diagnostic criteria are also a contributing factor. The adverse outcomes associated with pre-gestational diabetes are well known and have led clinicians to implement various strategies that include increased fetal surveillance and induction of labour at various gestational ages. In many cases these same strategies have been applied in clinical practice also to women with gestational diabetes despite there being differences in the type and magnitude of perinatal complications associated with this diagnosis. Despite the widespread application of these clinical practices, there is a paucity of quality data in the medical literature to guide the clinician in choosing a strategy for fetal surveillance and timing of delivery in both gestational diabetes and pre-gestational diabetes pregnancies. In the following review, we will discuss the rationale and consequences of planned delivery in gestational diabetes and pre-gestational diabetes, the evidence supporting different strategies for delivery and finally highlight future targets for research in this area.

Keywords

Diabetes, high-risk pregnancy

Rationale for labor induction in diabetic pregnancies

The goal of induction of labour in gestational diabetes (GDM) and pre-gestational diabetes (PGDM) pregnancies has traditionally been to prevent stillbirth or prevent excessive fetal growth and its associated complications. These benefits need to be weighed against the potential for increased Cesarean section (CS) rates, increased neonatal morbidity and increased health care costs.

Perinatal mortality

It is well known that there is an increase in perinatal mortality (PNM) in pregnancies complicated by PGDM – both type 1 and type 2 diabetes. The magnitude of this risk has decreased dramatically in the past several decades but is still in excess of that found in non-PGDM pregnancies.[1,2] Whether improvements in management of diabetes, increased fetal surveillance or the common practice of early delivery are the reason for the improved perinatal outcomes is unknown, but all are likely to have had a role in this achievement. Discussion of the relationship between glycemic control and increased fetal surveillance and PNM is beyond the scope of this review and we will instead focus on the role of early delivery in decreasing the risk of PNM. When discussing timing of delivery one must take into account the potential of decreasing stillbirth by early delivery versus the increased risk of neonatal morbidity and mortality that is inherent with earlier gestational age births. Ideally, induction of labour would take place at a gestational age that offers the highest yield in terms of stillbirth prevention while ensuring the minimum number of excess neonatal complications. From a purely neonatal perspective, recent population-based data suggest that the optimal timing of delivery might be between 39 and 40 completed weeks of gestation.[3–5] But will delivery at this gestational age prevent diabetes-related stillbirth? To answer this, one must explore the ''natural history'' of stillbirth in diabetic pregnancies. In a Danish study examining stillbirths in pregnancies complicated by Type 1 diabetes,[6] the average gestational age at the time of stillbirth was 33 weeks with a median of 35 (24–38) weeks. Importantly, 64% of the stillbirths occurred before 36 weeks of gestation and 40% prior to 34 weeks. Of the 25 cases of stillbirths, in almost half the cause of stillbirth was unknown although poor glycemic control was prevalent and a possible contributory cause. Based on these data it appears evident that a strategy of delivery at 36–38 weeks will still not prevent the majority of stillbirths. The role of better glycemic control and increased surveillance cannot be determined based on this study, but it is sobering to note that in 20/25 stillbirths the mother was examined by a health care professional within a week of the stillbirth. These data are in agreement with a large audit of stillbirths in type 1 and type 2 diabetes in the United Kingdom[7] where almost 80% of the stillbirths occurred at $\leq$36 weeks of gestation. One must remember, though, that it is difficult to assess the true natural history of type 1 and type 2 diabetes pregnancies after 38 weeks of gestation due to the confounding influence of the prevalent practice of planned delivery at 38 weeks of gestation.[8] It is possible that delaying delivery to a later gestational age would increase late stillbirths, but there is little evidence to quantify this effect. The evidence regarding stillbirth in GDM pregnancies is even less robust. Although earlier studies reported excess stillbirth in GDM pregnancies,[9–11] this has not been shown in more recent studies, including randomized controlled trials (RCTs) comparing treatment versus routine care.[12–15] In a recent retrospective analysis of population-based data from California, Rosenstein and colleagues[16,17] show that the overall risk of stillbirth from 36 to 42 weeks was higher in women with GDM when compared with women without diabetes (17.1 vs. 12.7/10,000 deliveries; RR 1.34, 95% CI 1.2–1.5). Stillbirth rates were also examined at each gestational age, and from 36 to 39 weeks, women with GDM had a statistically significant elevated RR of stillbirth compared with women without GDM, ranging from RR, 1.45 (95% CI, 1.1–1.9) at 38 weeks to RR 1.84 (95% CI 1.5–2.3) at 37 weeks. These increased risks did not remain statistically significant after 38 weeks of gestation, possibly due to the increase in stillbirths in non-GDM pregnancies or due to the impact of the practice of planned delivery after 38 weeks in GDM pregnancies but not in non-GDM pregnancies. The retrospective nature of this study and the inability to control for glycemic control and insulin treatment limits the ability to formulate practice guidelines from these data.

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Prevention of macrosomia

A second argument in favor of planned delivery in diabetic pregnancies is the potential benefit of reducing the risk of excessive fetal weight gain. It is well known that there is an association between excessive fetal weight and a multitude of perinatal complications including PNM,[18] shoulder dystocia and birth trauma,[19–22] and Cesarean delivery.[23–26] Earlier delivery will quite obviously lead to a reduction in birth weight as it will avoid the fetal weight gain that occurs in all pregnancies and likely to a greater extent in diabetic pregnancies.[27] Whether this will lead to a concomitant reduction in the risk of these birth weight–related complications has yet to be established. A recent Cochrane library study reviewed the utility of induction of labour for suspected macrosomia (defined as estimated fetal weight >4000 g) in non-diabetic pregnancies.[28] Three studies involving 372 women were identified where women were randomized to induction of labour or expectant management when the sonographic estimated fetal weight was above a predetermined threshold. In one of the studies, a policy of elective CS was in place when the estimated fetal weight was >4500 g. The pooled data reveal no difference in Cesarean delivery (RR 0.96, 95% CI 0.67 to 1.38), instrumental delivery (RR 1.02, 95% CI 0.60 to 1.74) or shoulder dystocia (RR 1.06, 95% CI 0.44 to 2.56). An inherent and currently unavoidable limitation of making delivery decisions based on estimated fetal weight is the poor performance of all methods of pre-delivery fetal weight estimation.[29–31] A recent study,[32] using a novel approach, collected retrospective National Vital Statistics data from the USA to create a model that would compare the effect of expectant management versus induction of labour in nulliparous women that had no recorded complications of pregnancy and gave birth to a macrosomic infant. The authors found that induction at 39, 40 and 41 weeks of gestation compared to expectant management led to a lower risk of CS (adjusted odds ratio 1.25 (1.17-1.33); 1.31 (1.23-1.4); 1.16 (1.06-1.28), respectively). Obviously, the use of retrospective data and the inability of the clinician to use birth weight to guide clinical decisions limit the applicability of this study to clinical practice. There is only one RCT that provides data comparing induction versus expectant management in diabetic pregnancies and this will be discussed in further detail later in this review.

A basic question that needs to be addressed before we can attempt to resolve the issue of timing of delivery in diabetic pregnancies is whether there are inherent risks associated with the act of inducing labour.

Risks associated with labor induction

The increasing rate of labour induction, involving more than 20% of pregnancies in developed countries,[33,34] has stimulated the investigation of possible risks associated with this intervention. Perhaps, the most suitable model for assessing the effects of labour induction per se on pregnancy outcome is elective labor induction which refers to induction in the absence of any maternal or fetal indications. The main focus of most of the studies addressing this issue was the effect of labour induction on risk of CS.[35–42] Other potential concerns associated with labour induction include fetal distress due to uterine hyperstimulation, chorioamnionitis and neonatal respiratory morbidity when induction takes place prior to 39 weeks of gestation.[35,37,43–46]

Labor induction and the risk of CS

The general view is that labour induction increases the risk of CS.[38] This concept is mainly based on the findings from observational cohort studies which compared the outcome of women undergoing labor induction to that of women with spontaneous onset of labour.[35–37,39–42,44,47–54] Most of these studies reported that women who undergo labour induction are at an increased risk for CS compared to women with spontaneous onset of labour. In a recent systematic review and meta-analysis of observational studies, elective labor induction was found to be associated with an approximate 50% increase in the risk for CS compared with spontaneous delivery.[55] However, a major limitation of many of these studies is the lack of information regarding the cervical Bishop's score at the time of induction, which is strongly correlated with the likelihood of successful induction.[56–58] Although some of these studies have considered the need for pre-induction cervical ripening as a surrogate for a low Bishop's score, there is still a major potential for selection bias as physicians are more likely to recommend labour induction in the presence of a favorable cervix.

Other investigators have criticized the methodological approach taken by most of the observational studies, arguing that in practice the clinical dilemma faced by clinicians and patients is not choosing between labor induction or spontaneous delivery but instead between labor induction or expectant management.[56,59] Thus, the control group used by most of the RCTs and few of the observational trials investigating the outcome of elective labour induction included women who underwent expectant management, taking into account the fact that a certain proportion of women who are managed expectantly will eventually undergo labour induction or CS for other reasons including post term or other maternal or fetal indications. Overall, most of these studies have found that elective labour induction is associated with a similar or even lower risk for CS compared with expectant management.[59–69] In a recent systematic review and meta-analysis of RCTs, elective labour induction was found to be associated with about 18% decrease in the risk of CS compared with expectant management ($p = 0.003$).[55] Nevertheless, it should be emphasized that most of these studies included women at or beyond 41 weeks. Only three RCTs that compared labour induction at less than 41 weeks with expectant management were identified.[63,64,70] Although these latter studies did not detect a significant difference in the risk of CS between induction at less than 41 weeks and expectant management, these studies were of relatively small sample size and are less applicable to the current practice as they were conducted between 1975 and 1989. Thus, high-quality data regarding the consequences of labour induction versus expectant management at less than 41 weeks is lacking.[55] Furthermore, the interpretation and applicability of many of the studies included in the meta-analysis described above[55] is limited by the considerable differences in clinical practice and baseline CS rates between different countries and between different time periods (1975 through 2005).

Because of the concerns regarding the increased risk for CS, a large number of studies have investigated factors that are associated with induction failure or success.[57,58,71] The two most commonly studied factors are cervical status (usually reflected by the Bishop's score) and parity.[39,54,57,58] Other factors include maternal age,[39,72] maternal body characteristics (e.g. body mass index),[39,72–74] gestational age[75] and neonatal birth weight.[38,39] Although sonographic cervical length[76–79] and fetal fibronectin have been also shown to be associated with the likelihood of induction failure, it has been suggested that they are not superior to the Bishop's score.[57] Several prediction models have been generated based on these factors to assist clinicians in stratifying the risk of induction failure.[80,81] However, prospective external validation of these models have yielded only moderate predictive value with the area under the ROC curve ranging from 0.59 to 0.76.[71,82]

Neonatal risks associated with labor induction

Labour induction also carries potential risks for adverse neonatal outcome. The association of labour induction, especially using prostaglandins, with uterine hyperstimulation and non-reassuring fetal heart rate is well documented[83] and is probably more frequent with misoprostol than with prostaglandin E2.[84] In addition, the longer duration of labor following induction[85,86] and the use of mechanical rather than pharmacological methods for labour induction might increase the risk of chorioamnionitis and neonatal infection.[87]

Nevertheless, a meta-analysis of RCTs and observational studies failed to detect significant differences in the rates of fetal asphyxia, maternal or neonatal infectious morbidity, or neonatal admission to the intensive care unit between the induction and expectant management groups, even though the overall strength of evidence was low.[55] In fact, in the largest RCT comparing labour induction with expectant management of pregnancies of 41 or more weeks' duration, labour induction was actually associated with a lower rate of CS due to fetal distress.[61]

Another potential concern is the increased risk for neonatal morbidity, especially respiratory difficulties, when induction takes place at less than 39 weeks.[88] This concern is of even more relevance in cases in which gestational age is not well validated. For that reason, the American College of Obstetrics and Gynecology (ACOG) recommends that no elective delivery should be performed before the gestational age of 39 weeks.[89]

Risks of labour induction – summary

Current evidence suggest that although labour induction is associated with a higher risk for CS compared with deliveries with spontaneous onset, when a more realistic control group is used, that is expectant management, labour induction does not seem to increase the risk of CS. One of the reasons for this observation is that a considerable proportion of women who are managed expectantly will eventually require labour induction or CS for other indications. In addition, the increase in fetal weight, decrease in amniotic fluid and placental aging associated with expectant management might increase the need for intrapartum CS due to dystocia or non-reassuring fetal heart rate among women who are being managed expectantly.[55,61] Importantly, while these observations relate to the overall population included in these studies, the effect of labour induction on the risk of CS compared with expectant management in the individual case should be adjusted based on the cervical status and other factors associated with successful induction, as well as the likelihood of need for labour induction at a later stage of pregnancy due to maternal or fetal conditions.

There are other potential maternal or neonatal risks that are associated with labour induction such as maternal or neonatal infection and fetal distress. However, these concerns are not supported by data from RCTs.

Finally, another disadvantage of labour induction that should be taken into consideration is the adverse effect on maternal birth experience.[90,91] Women who underwent labour induction were found to have a less positive birth experience and were less satisfied with their labour process.

Labor induction versus expectant management in diabetic pregnancies – current evidence

We discussed above the possible benefits of induction of labour in pregnancies complicated by diabetes, however, prior to translation into clinical practice this needs to be confirmed with experimental data. Furthermore, the general risks associated with labour induction that were described above may be less applicable to diabetic pregnancies that are confounded by higher birth weight and maternal obesity, which are likely to affect the risk of CS in cases of labour induction. In addition, the risk of neonatal respiratory morbidity when induction takes place prior to 39 weeks may be even higher in diabetic pregnancies, especially in the presence of poor glycemic control.[92] Thus, the optimal balance between the benefits and risks of labour induction in diabetic pregnancies can be only determined empirically. Unfortunately, few studies on labour induction versus expectant management in diabetic pregnancies are available (Table 1), only one of which is an RCT.

Types of intervention thresholds

There are basically two types of thresholds that can be used for timing of elective delivery in diabetic pregnancies – a gestational age- and an estimated fetal weight (EFW)-based threshold. While the rationale for using a gestational age-based threshold is mainly to reduce the risk of sudden fetal death, the use of an EFW-based threshold is mainly focused in reducing the risks associated with fetal macrosomia, namely shoulder dystocia and CS.

Studies with a gestational-age-based threshold for intervention

The only RCT comparing elective induction with expectant management in pregnancies complicated by diabetes was published by Kjos et al.[93] in 1993 (Table 1). In this study, the authors randomized 200 women with uncomplicated insulin-requiring diabetes (187 with GDM and 13 with type 2 diabetes) to labour induction at 38 weeks of gestation or expectant management. The expectant management group was monitored with weekly physical examination and twice-weekly nonstress tests and amniotic fluid volume estimation until delivery, 42 weeks of gestation or EFW > 4200 g. Only women with good glycemic control, good compliance and an EFW < 3800 g were included in the randomization. Analysis was done by an intention-to-treat approach. The baseline characteristics of the two groups were similar. The proportion of women who underwent labour induction was 70% and 49% in the induction and expectant groups, respectively. Compared with expectant management, induction of labour at 38 weeks was associated with a lower gestational age at delivery and a lower birth weight as reflected by a lower mean birth weight and a lower rate of macrosomia and Large for Gestational Age (LGA) infants (Table 1). However, there were no differences in the rate of CS, shoulder dystocia, PNM and neonatal morbidity between the two groups (Table 1). Thus, although macrosomia and LGA may be associated with long-term morbidity,[94–96] this study did not detect any differences between the two approaches with regard to direct measures of maternal and neonatal mortality and morbidity. The main limitations of this well-designed study are the small sample size and its heterogeneous population, including both women with GDM and PGDM. The main rationale for using a gestational age-based threshold would be to decrease the risk of fetal death, however this study was not powered for such an outcome, especially in this subgroup of well-controlled diabetic women with appropriate for gestational age (AGA) fetuses. The lack of significant difference in the CS rate between the two groups could be attributed, at least in part, to the fact that almost half (49%) of the women in the expectant management group eventually required induction of labour. Finally, results that were published some 20 years ago might not be applicable today as changes in antenatal care and fetal health surveillance would likely influence study outcomes.

In another study, Lurie et al.[97] analyzed the impact of a new management protocol for diabetic pregnancies – routine induction of labour at 38 to 39 weeks – on pregnancy outcome (N = 96). Data were compared with a historical control group that was managed based on a previous protocol, according to which labour was induced in cases of EFW > 4000 g (N = 164) (Table 1). Cases with an EFW > 4500 g underwent elective CS in both time periods. The authors found that the new, gestational age-based-protocol was associated with a lower gestational age at delivery (38.4 vs. 39.2, Table 1). However, there were no significant differences between the two groups with respect to the rate of CS, shoulder dystocia, birth weight, rate of macrosomia or neonatal mortality or morbidity (Table 1). Thus, the only consequence of using a gestational age-based threshold (new protocol) rather than an EFW-based threshold (old protocol) was a lower gestational age at delivery. In a second analysis, the authors compared the study group to the subgroup of women in the historical control group who delivered at >40 weeks (n = 62). In this latter analysis, which more closely simulates comparison between induction

Table 1. Studies comparing active vs. expectant management in diabetic pregnancies.

Ref	Design	Study group	Control group	GA (wks)	CS (%)	SD (%)	Birth weight	Neonatal outcome	Comments
Kjos et al.[93]	RCT (1987–1991)	Induction at 38 w (N = 100)	Induction at 42 w or EFW > 4200 g (N = 100)	39 vs. 40 ($p < 0.05$)	25 vs. 31 (p = NS)	0 vs. 3 (p = NS)	3446 g vs. 3672 g ($p < 0.001$) > 4000 g: 15% vs. 27%, $p = 0.05$ LGA: 10% vs. 23% ($p < 0.01$)	Mortality: 0% vs. 0% Hypoglycemia: 0% vs. 0%	Inclusion criteria: - Good glycemic Control - EFW < 3800 g Limitations: - 49% in control group underwent induction - Limited power (IUFD)
Lurie et al.[97]	Cohort (1983–1994)	Protocol: Induction at 38 w (CS if EFW > 4500 - g) N = 96	Historical control – Protocol: Induction if EFW > 4000 - g (CS if EFW > 4500 g) N = 164	38.4 vs. 39.2	22.9 vs. 18.9 (p = NS)	1.0 vs. 4.3 (p = NS)	3406 g vs. 3430 g (p = NS) > 4000 g: 9.4% vs. 18.3% (p = NS)	Mortality: 1.0% vs. 0.0% (p = NS) RDS: 0% vs. 0% Trauma: 0% vs. 1.8% (p = NS)	When historical control was limited to those delivered after 40 w ("expectant") - less SD (10.2% vs. 1.4%), less macrosomia (9% vs. 24%) Limitations: Limited power No adjustment for confounders No data on glycemic control Temporal changes

(continued)

Table 1. Continued

Ref	Design	Study group	Control group	GA (wks)	CS (%)	SD (%)	Birth weight	Neonatal outcome	Comments
Conway and Langer[99]	Cohort (1990–1995)	Protocol: Induction if susp. LGA at 37–38 weeks (CS if EFW > 4250 g) (N = 1377)	Historical control – before protocol (N = 1227)	39.2 ± 1.6 vs 39.3 ± 1.5 (p = NS)	25.1 vs. 21.7 (p < 0.04)	1.5 vs. 2.8 (p = 0.02)	> 4000 g: 9% vs. 12%, p = 0.04 LGA: 17% vs. 19% (p = NS)		Similar GA despite difference in protocol Limitations: Lack of adjustment for confounders Lack of data on glycemic control
Lurie et. al, 1992 [100]	Cohort (1983–1988)	Same protocol: induction if EFW > 4000 (CS if EFW > 4500 g) Delivery >40w (N = 65 GDMA1, 59 GDMA2)	Delivery <40w (N = 65 GDMA1, 59 GDMA2)	GDMA1 38.2 vs. 40.9 GDMA2 37.5 vs. 40.5	GDMA1 11 vs. 14 (p = NS) GDMA2 25 vs. 22 (p = NS)	GDMA1 0 vs. 3.6% (p = NS) GDMA2 4.6% vs. 2.2% (p = NS)	GDMA1 3439 g vs. 3617 g (p = NS) >4000 g: 15% vs. 25% (p = NS) GDMA2 3275 g vs. 3639 g (p = 0.003) >4000 g: 7% vs. 20% (p = NS)	GDMA1 Mortality: 0.0% vs. 0.0% RDS: 0 vs. 0 Trauma: 0% vs. 0% Hypoglycemia: 3% vs. 3% GDMA2 Mortality: 0.0% vs. 0.0% RDS: 0 vs. 0 Trauma: 2.3% vs. 4.4% (p = NS) Hypoglycemia: 10% vs. 8% (p = NS)	Groups matched by age and parity Limitations: Limited power Risk of selection bias No data on glycemic control No adjustment for confounders

EFW: estimated fetal weight; CS: Cesarean section; RCT: randomized controlled trial; GDM: gestational diabetes.

using a gestational age-based threshold versus expectant management (rather than induction using a EFW-based threshold), induction at 38 to 39 weeks was associated with a lower rate of macrosomia (9% vs. 24%, $p<0.05$) and shoulder dystocia (1.4% vs. 10.2%, $p<0.05$). This study is limited by the relatively small sample size and lack of adjustment for possible confounders including glycemic control. Furthermore, one major concern with respect to the second analysis is the potential risk of selection bias which should lead to caution in using these findings to guide clinical practice. Taking a different approach, Nicholson et al.[98] attempted to define an optimal time of delivery (OTD) based on maternal–infant outcomes. Using retrospective data from low- and high-risk pregnancies, including a subset of pregnancies complicated by diabetes, the authors calculated an OTD for diabetic pregnancies of $40+3-41+1$ weeks. Although reassuring for the proponents of expectant management, this study is limited by the inability to control for type of diabetes and the retrospective nature that likely favored milder diabetes being managed expectantly until later gestational ages.[98]

Studies with estimated fetal weight-based threshold for intervention

In a more recent and larger study, Conway and Langer[99] prospectively investigated the impact of a new EFW-based protocol for elective delivery of diabetic (both GDM and PGDM) women in their clinic. According to that protocol, the timing and mode of delivery of diabetic women was determined based on a sonographic EFW at 37 to 38 weeks. Women with an EFW > 4250 g underwent elective CS, those with suspected LGA fetus (EFW > 90th percentile) underwent labor induction and the others underwent expectant management. Outcome of this approach was compared with that of a historical control group of diabetic women prior to the adoption of this protocol and in whom no intervention was routinely taken based on accelerated fetal growth (Table 1). The new protocol was associated with a lower rate of macrosomia and an almost 50% decrease in the rate of shoulder dystocia (1.5% vs. 2.8%) with a relatively small increase in CS rate (25.1% vs. 21.7%) (Table 1). The authors concluded that this new EFW-based protocol achieves a considerable reduction in the rate of shoulder dystocia with a relatively small cost in terms of CS rate. The fact that the gestational age at delivery was relatively similar in the two groups is probably related to the fact that only 10.6% of the women who were managed based on the new protocol required any intervention (induction or CS), which is much lower than the intervention rate in the case of gestational age-based threshold (as described above). The main limitations of this study are the lack of clear information regarding the management approach prior to the implementation of the protocol and lack of adjustment for potential confounders including degree of glycemic control. In addition, the rates of neonatal morbidity and respiratory complications, which might be more common under such a protocol, were not reported in that study.

Finally, in an earlier retrospective study by Lurie et al.,[100] the authors reported the outcome of women with GDM who delivered at >40 weeks (n = 124). The outcome of this group was compared to a control group of women with GDM who delivered at <40 weeks, matched by maternal age and parity. During the study period, intervention was taken only based on EFW-threshold: women with an EFW > 4000 g underwent labor induction and those with an EFW > 4500 g underwent elective CS. Data were analyzed separately for women with GDMA1 (diet treated) and women with GDMA2 (insulin treated). The only difference between the two groups was a lower mean birth weight in the subgroup of women with GDMA2 who delivered prior to 40 weeks (Table 1). There were no differences between the two groups with regard to CS rate, shoulder dystocia, rate of macrosomia and neonatal morbidity. The authors' conclusion was that the timing of delivery does not have a significant impact on clinically important maternal or neonatal outcomes and that elective intervention prior to 40 weeks of gestation is to be avoided. Nevertheless, interpretation of these findings is limited by the sample size, the serious risk of selection bias and the lack of adjustment for potential confounders.

Summary

Overall, data on the risks and benefits of active versus expectant management of diabetic pregnancies are sparse with only one published RCT. The few observational studies are limited by being underpowered to address rare outcomes, lack of adjustment for potential confounders including glycemic control and Bishop's score, use of historical and not well-defined control groups, which may introduce bias due to temporal changes, and risk of selection bias. In addition, these studies provide only limited data on the risk of neonatal morbidity and respiratory complications, especially when induction takes place prior to 39 weeks of gestation. Finally, most of the women included in these studies were GDM patients so that the data available regarding patients with PGDM, in whom the risks of expectant management might be even higher, are even more limited (only 6.5% of the patients in the study of Kjos et al.[93] and 8.7% of the patients in the study of Conway and Langer[99]).

In a recent systematic review on this topic,[101] the authors concluded that given the substantial heterogeneity in the studies it was not possible to provide any quantitative synthesis of the data and that the authors were limited in their ability to draw definite conclusions.

Conclusion

In the current paper, we discussed the potential benefits and risks of elective delivery versus expectant management in pregnancies complicated by gestational and pre-gestational diabetes. Such an intervention may be based on gestational age or sonographic EFW, with the second option being limited by the inherent inaccuracy of sonographic EFW, especially in cases of suspected macrosomia.[31] To date, data in support of any of these approaches are extremely limited. The available studies are underpowered to address the effect of elective delivery on the risk of fetal death, which is probably one of the main reasons for adopting an approach of routine elective induction based on gestational age alone. Other clinical factors such as the type of diabetes, degree of glycemic control, degree of growth asymmetry (e.g. AC/FL ratio) and Bishop's score have not been incorporated in the management protocols investigated in these studies.

The absence of such evidence has also resulted in a considerable variation in the recommendations of the different societies.[102] We believe that with a lack of solid evidence to justify routine intervention based on any type of threshold, the decision on elective delivery should be made on an individual basis, taking into account a number of clinical factors including gestational age, sonographic and clinical estimated fetal weight, type of diabetes, degree of glycemic control, obstetrical history of the individual patient (e.g. a history of stillbirth) as well as parity and cervical status. The potential benefits and risks of elective delivery should be discussed with the patient, and patient preference following such a discussion should also be included in the final decision on elective delivery.

It is also critical to distinguish GDM from PGDM pregnancies when deciding on the timing of delivery. Though often treated similarly, the risk of stillbirth is dramatically different. In PGDM the goal of early delivery is mainly to prevent stillbirth without significantly increasing the risk of neonatal morbidity. In these cases a policy of starting to plan the delivery at 38 weeks of gestation is logical although not evidence based. In GDM pregnancies the main goal is to prevent delivery complications i.e. Cesarean delivery and birth trauma. With little evidence to guide us, using common "Obstetric sense" might be the only course to follow. The poorly controlled GDM with a PGDM phenotype (elevated BMI, marked insulin resistance as manifested by insulin requirements, polyhydramnios and increased fetal abdominal

circumference) should likely be managed more conservatively with consideration towards earlier induction. Conversely, the "low risk" well-controlled primiparous GDM patient with an unfavourable cervix is likely to benefit from expectant management. Although commonly used by practitioners, the distinction between insulin-treated and diet-treated GDM pregnancies should not necessarily be the sole criterion used when deciding on timing of delivery. In our practice, we routinely expectantly manage patients with GDM until 40 weeks of gestation if they are well controlled on a low dose of insulin and have no sonographic evidence of abnormal fetal growth patterns (i.e. increased abdominal circumference) or polyhydramnios. The fact that we are basing our delivery decisions in pregnancies complicated by diabetes on such a fragile platform of scientific evidence is disturbing but should be leveraged towards a global effort to obtain this much needed evidence.

Several studies on elective delivery in diabetic pregnancies are currently ongoing. The GINEXMAL study[103] is an ongoing multicenter international RCT comparing induction of labour at 38–39 weeks of gestation to expectant management, with CS rate being the primary outcome measure. A significant limitation of this study is the exclusion of women with suspected macrosomia. Another ongoing RCT compares induction of labour at 38 weeks with induction of labour at 40 weeks in patients with Insulin dependent GDM.[104] Further prospective RCTs are necessary in order to provide additional high-quality data regarding the optimal thresholds for intervention in diabetic pregnancies. Ideally, these data would come from a RCT comparing induction of labour at 38 weeks of gestation with expectant management until 40 weeks of gestation. The study should enroll women with both diet- and insulin-treated GDM and while ultrasound data should be collected, EFW should not be used as an exclusion criterion. The study would need to be powered to assess significant maternal and neonatal outcomes and allow for subanalyses by method and adequacy of glycemic control. Until such data are available, the clinician should consider the maternal, fetal and neonatal implications of induction of labour versus expectant management, involve the patient in the decision process and as usual follow the maxim of "first do no harm."

Conflict of interest

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Contributorship

Both Howard Berger and Nir Melamed contributed equally to the conception and design of the paper, acquisition and interpretation of data, drafting of the review and have provided final approval of the version to be published.

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